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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/658,602	09/08/2003	Enrique Zudaire Ubani	701779	6049
45733 7590 02/21/2008 LEYDIG, VOIT & MAYER, LTD. TWO PRUDENTIAL PLAZA, SUITE 4900 180 NORTH STETSON AVENUE CHICAGO, IL 60601-6731			EXAMINER SIMS, JASON M	
			ART UNIT 1631	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary**Application No.**

10/658,602

Applicant(s)

ZUDAIRE UBANI ET AL.

Examiner

JASON M. SIMS

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 November 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 9,12,15-18,20,21,23,26-28,85,87 and 90-114 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 9,12,15-18,20,21,23,26-28,85,87 and 90-108 is/are rejected.
- 7) ☒ Claim(s) 109-111 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/13/2008 has been entered.

Applicant has newly added claims 97-114 in the response filed 11/13/2007, which have been acknowledged and entered.

Applicant's cancellations of claims 11, 13-14, 22, 24-25, 86, and 88-89 in the response filed 11/13/2007 is acknowledged.

Claims 9, 12, 15-18, 20-21, 23, 26-28, 85, 87, and 90-114 are the current claims hereby under examination.

The following objection is being newly applied and has been necessitated by amendment:

Claim Objections

Claims 106-108 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

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The following rejection is being newly applied and has been necessitated by amendment:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 103-105 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 103-105 comprise the wording "are the only emission readings of the double stranded DNA intercalating dye," which has been deemed as vague and indefinite. It is unclear if the wording is suppose to indicate some type of filtration wherein the emission readings do not comprise any background noise, but are indeed strictly only the emission reading coming from the intercalating dye itself or that there are only two emission readings performed during each thermal cycle. For the purposes of examination it has been interpreted as there are only two emission readings performed during each thermal cycle. Clarification via claim wording is required.

Claim Rejections - 35 USC § 102

Response to Arguments:

Applicant's arguments, filed 11/13/2007, with respect to the claims rejected under 35 USC 102 (e) have been fully considered and are persuasive because of applicant's amendments to the claims. Therefore the rejection has been withdrawn.

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The following rejection is being newly applied and has been necessitated by amendment:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 9, 12, 15-18, 20-21, 23, 26-28, 85, 87, 90-99, and 100-105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wittwer et al. (US P/N 6, 472,156) in view of Loffler et al. (US P/N 2003/0186259).

The claims are directed to a method of real-time detecting and quantifying a first nucleic acid template and a second nucleic acid template in a PCR mixture comprising the steps of thermally cycling a PCR mixture, obtaining first and second emissions, and determining the first and second emission amounts.

Wittwer et al. teaches limitations of claims 9, 21, 85, 97-99, and 103-105 at col. 1, lines 13-22, col. 2, lines 25-67 and col. 3, lines 1-37, col. 3, lines 40-67, col. 4, lines

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1-18, lines 31-35, lines 42-47. Wittwer et al., at col. 1, discusses how the invention relates to multiplex PCR using differential fluorescent emission and differential hybridization melting temperatures, which allows simultaneous analysis. Wittwer et al., at col. 2 and col. 3, discusses step a of claims 9, 21, and 85 a thermal cycling method, using a thermostable polymerase, dyes that bind to double stranded DNA and multiple primers and probes for amplifying multiple sequences of DNA. Wittwer et al. further teaches at col. 3, lines 4-7 and col. 17, lines 1-18 using a double stranded DNA intercalating dye. Wittwer et al. discusses, step b of claims 9, 21, and 85 at col. 3 and col. 4, using at least 2 probe pairs where one member of each pair differentially hybridizes to different alleles and measuring the emission of each of the members at a first temperature and repeating those emission measurements at a second and third temperature, which represents obtaining cycle by cycle at a first MT and a second MT the emissions and also reads on intermittently obtaining emission readings during each cycle. Wittwer et al. further discusses part c of claims 9, 21, and 85 in col. 4 at lines 28-35 and 42-47, the different hybridizations having different emissions at different Tms and determining the different emissions based on the different Tms, which represents determining cycle by cycle a first emission amount and a second emission amount. Wittwer et al. at col. 3, lines 40-67 and col. 4 as discussed above teaches taking emission readings at first and second temperatures through each thermocycle, which reads on the first emission and the second emission are the only emission readings of the double stranded intercalating dye obtained during each thermal cycle.

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Wittwer et al. teaches limitations of claims 12, 23, and 87 at col. 3, lines 4-7.

Wittwer et al. discusses the background to PCR using nucleic acid binding dyes such as ethidium bromide and SYBR Green I, which are double stranded DNA intercalating dyes.

Wittwer et al. teaches limitations of claim 24 at col. 11, lines 66-67 and col. 12, lines 1-5. Wittwer et al. discusses using a PCR primer as a "probe-primer," which represents the double stranded DNA dye as being a primer-based double stranded DNA dye.

Wittwer et al. teaches limitations of claim 25 at col. 12, lines 15-20. Wittwer et al. discusses acceptable fluorophore pairs for use as fluorescein and rhodamine among others.

Wittwer et al. teaches limitations of claims 15-18, 26-27, 90-94, and 96 at col. 15, lines 60-67 and col. 16, lines 1-45. Wittwer et al. discusses emission measurements being made every 50 to 10,000 msec and the temperature between measurements varying by 0.01 degrees Celsius per second to 5 degrees Celsius per sec or varying by 0.5 or 1.0 degrees Celsius per second. Wittwer et al. discusses how initial temperatures for initial emission measurements are made at low temperatures and subsequent emission measurements are made at higher temperatures until at least melting temperatures. Therefore the increased increments of temperature ranges ensures at least 3 or more emission measurements, which represents increasing the temperature at which emission measurements are taken in the markush ranges specified in the instant claims.

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Wittwer et al. teaches limitations of claims 20, 28, and 95 at col. 25, lines 65-67.

Wittwer et al. discusses using the Lightcycler software for PCR and melting curve analysis, which represent a computer program for calculating first and second emissions.

Wittwer et al. suggests, but does not explicitly teach the limitation of quantifying the first and second amplicons as in step C of claims 9, 21, and 85. Wittwer et al. suggests this embodiment in the invention by stating at col. 11, lines 2-3 and col. 17, lines 20-23 the use of multiplexing and the use of hybridization probes as a means for quantification. Therefore, Wittwer et al. recognizes that quantifying the amplicons using the methods within the invention is possible and within the scope of one of ordinary skill in the art.

Loffler et al. specifically teaches at paragraph [0014] that the extent of fluorescence during FRET is directly proportional to the amount of target DNA, which is generated during the PCR process. Loffler et al. teaches that as a result of this, the increase in DNA produced can be monitored via an increase in the fluorescence signal. Furthermore, Loffler et al. at paragraph [0039] teaches that the emission being detected not only identifies the amplicon, but also enables quantification of the amplicon in the reaction solution.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to quantify the amplicons during each cycle in the PCR reaction because Wittwer et al. states that the methodology of using the hybridizable probes in

FRET can be used for quantification and Loffler et al. specifically teaches how quantification is done using hybridizable probes in FRET analysis.

Wittwer et al. does not specifically teach wherein the first and second amplicons have melting curves, which do not overlap as in claims 100-102.

However, Wittwer et al. does teach being able to analyze multiple sequence samples simultaneously and at Fig. 1 gives examples of the different melting curves for three samples. It would have been obvious to one of ordinary skill in the art at the time to apply the known method taught by Wittwer et al. to samples or amplicons, which do not overlap in their melting curves because analyzing samples or amplicons without overlapping melting curves would have been a simple substitution of some components. It is well known that different sequences have different melting curves as discussed throughout the invention by Wittwer et al. col. 17, lines 1-18. Therefore, it is obvious to one of ordinary skill in the art at the time of the instant invention that one could have substituted one known element, which are amplicons with melting curves that do not overlap, with the known method for performing hybridization analysis and the results would have been predictable.

Allowable Subject Matter

Claims 109-111 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

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No claim is allowed.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jason Sims, whose telephone number is (571)-272-7540.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Marjorie Moran can be reached via telephone (571)-272-0720.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the Central PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The Central PTO Fax Center number is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

// Jason Sims //

 15 February 2006
JOHN S. BRUSCA, PH.D
PRIMARY EXAMINER